immune responses in the cases of various autoimmune diseases.

[PC1-1] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Apoptotic potential of Apicidin and its derivatives

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We previously reported that apicidin, a histone deacetylase (HDAC) inhibitor, arrests human cancer cell growth through selective induction of $p21^{WAF1/Cip1}$. In this study, the ability of apicidin and its derivative to induce apoptosis was evaluated. HL60 cell growth was completely arrested at G_2/M phase by treatment with apicidin and its derivative, which was correlated with marked induction of $p21^{WAF1/Cip}$ protein. These effects were paralleled by increase in cell death, nuclear morphological change, DNA ladder and apoptotic body formation. Furthermore, this apoptotic cell death was accompanied by conversion of the proenzyme form of caspase-3 to the catalytically active effector protease and subsequent cleavage of poly(ADP-ribose)polymerase and DFF45 (DNA fragmentation factor), one of the caspase-3 target. Taken together, these results suggest that apicidin and its derivative-induced apoptosis might be, in part, due to the activation of caspase-3

[PC1-2] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Effects of histone deacetylase inhibitor, apicidin, on the p21WAF1/Cip1 gene promoter

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We previously reported that apicidin, a histone deacetylase inhibitor, showed a broad spectrum of antiproliferative activity against various cancer cell lines through selective induction of $p21^{WAF1/Cip1}$, which plays important roles in the cell cycle. In this study, we examined the effects of apicidin on $p21^{WAF1/Cip1}$ gene promoter in a p53-mutated HeLa cells. $p21^{WAF1/Cip1}$ mRNA was markedly induced by treatment with 0.01μM apicidn, and dramatic $p21^{WAF1/Cip1}$ protein induction was detected. Using human wild-type $p21^{WAF1/Cip1}$ promoter, we found that apicidin strongly activates the $p21^{WAF1/Cip1}$ promoter in a dose and time dependent manner. Futhermore, the Sp1-luc plasmid containing SV40 promoter-derived three consensus Sp1 binding sites was markedly activated by apicidin. Theses results suggest that apicidin arrests the growth of HeLa by activating the $p21^{WAF1/Cip1}$ promoter through specific Sp1 sites in a p53-independent fashion.

[PC1-3] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Chemopreventive potential of the synthetic allylthiopyridazine derivatives on hepatocellular carcinoma cells

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Dietary organosurfur compounds including diallylsulfide, a component of garlic oil, have been shown to inhibit proliferation of tumar cells and suppress chemically-induced carcinogenesis in experimemtal animals. Since hepatocellular carcinoma is one of the most lethal malignancies and there is no effective preventive measure in this highly malignant disease to date, we wished to pursue the chemopreventive potential of the synthetic allylthiopyridazine derivatives (K compounds) on SK-Hep-1 hepatocarcinoma cells. Here, we report that the K compounds efficiently inhibited SK-Hep-1 cell proliferation through induction of apoptosis. Increased chain length at the 3-position of allylthiopyridazine ring improved potency of growth inhibition(3-propoxy>3-isopropoxy>3-ethoxy>3-methoxy>3-chloro derivatives).
Expression of the anti-apoptotic oncoprotein Bcl-2 was prominently decreased whereas the death-promoting Bax expression remained unchanged or slightly upregulated during the apoptosis precess in SK-Hep-1 cells treated with K compounds. We also provide evidence that the K compound-induced apoptosis involves cytochrome c release and caspase-3 activation. these resuls suggest that the allylthiopyridazine derivatives induce apoptosis in SK-Hep-1 hepatocarcinoma cells through a caspase-3-dependent mechanism, which may contribute to the chemopreventive function of these agents for hepatocellular carcinoma.

[PC1-4] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Study on the antiproliferative effects of apicidin derivative in tumor cell lines

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Apicidin is a fungal metabolite shown to exhibit antiparasitic activity by the inhibition of histone deacetylase (HDAC). In this study, we evaluated apicidin derivative as a potential antiproliferative and detransforming agent. Treatment of HeLa cells with apicidin derivative resulted in morphological change, inhibition of HDAC *in vivo* and *in vitro* and cell cycle arrest at G_0/G_1 and G_2/M phase. Also, apicidin derivative showed a broad spectrum of antiproliferative activity against various cancer cell lines even though with differential sensitivity. In addition, apicidin derivative increased the expression of cyclin dependent kinase inhibitor, $p21^{WAF1/Cip1}$ and gelsolin which controls the length of actin stress fibers. Specially, the elevated levels of $p21^{WAF1/Cip1}$ led to decreased Rb phosphorylation. These results suggest that induction of histone hyperacetylation by apicidin derivative is responsible for the antiproliferative activity through selective induction of genes, which play important roles the cell cycle and cell mophology.

[PC1-5] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Alteration of antioxidant enzymes in response to oxidative stress and antioxidants

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The induction of apoptosis by oxidative stress and the activity of antioxidant enzymes were investigated in SK-MEL-2 cells treated with hydrogen peroxide(H2O2). Cisplatin known to generate oxygen species was added to cells and the induction of apoptosis and the antioxidant enzyme activity were measured. The effects were compared with the results obtained H2O2 treated cells. After pretreatment with vitamin E and selenomethionine, SK-MEL-2 cells were exposed to H2O2 determine the effect of antioxidants on apoptosis. Also, H2O2 and cisplatin were concomitantly treated and the changes in apoptosis and the activity of antioxidant enzyme were investigated. The cell viability at 2.5mM H2O2 was declined gradually for 24 hrs and superoxide